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**14. ABSTRACT**

This report describes the first year of a project to design and construct multileaf collimators (MLC) to be used in proton radiotherapy. This research project is a joint collaborative effort between the University of Pennsylvania (HUP) and the Walter Reed Army Medical Center (WRAMC) and is part of a larger project to build a state-of-the-art proton radiotherapy facility in Philadelphia in collaboration with the Children's Hospital of Philadelphia (CHOP).

The accomplishments during the start-up phase in the first year of the project are described in this report. (1) Assemble personnel required to perform the tasks listed in the Statement of Work, (2) Establish an efficient working relationship with the Radiation Therapy group at WRAMC, (3) Install the Monte Carlo simulation code GEANT4 and validate our use of it using published data, (4) Study, using GEANT4 and published data, the neutron production from and activation of MLCs made of different materials (e.g. tungsten, iron, and brass) to determine the optimal choice of material for patient and personnel safety, (5) Commence requirements definition process for remote telemedicine, and (6) Initial work on setting up a Web-based system to enroll patients into proton therapy clinical trials.

**15. SUBJECT TERMS**
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## Introduction

The overall goal of this multi-year research project in collaboration with the Walter Reed Army Medical Center is to develop the necessary tools to make the proton facility, which is to be constructed in Philadelphia as part of joint facility with the Children's Hospital of Philadelphia, the most advanced proton radiotherapy center. The first tool being developed, and what will be described in this report, is the development of a multileaf collimator (MLC) for proton therapy. The use of multileaf collimators in conventional radiation therapy, initially as a time and labor saving device, is the basis for a dramatic change in the delivery of radiation therapy. MLCs and advances in computer-controlled systems allowed the intensity of radiation fields to be easily modulated in two dimensions and led to what is called intensity modulated radiation therapy (IMRT), where dozens or even hundreds of sub-fields are used. IMRT has become the most widely available method to deliver conformal radiation therapy. Proton therapy has the potential to deliver more conformal treatment because of its low entrance dose and sharp falloff beyond the Bragg peak. However, as is the case for photon treatments, higher conformation is achieved as the number of fields in a treatment plan increases. Without an MLC it is difficult to deliver a large number of proton fields efficiently. This research investigates the issues that must be resolved to use an MLC in proton therapy. This report describes the initial stages of that project, performed during the first year, including the following activities and achievements: (1) Assemble critical personnel required to perform the tasks listed in the Statement of Work, (2) Establish an efficient collaborative working relationship with the Radiation Therapy group at WRAMC, (3) Install the Monte Carlo simulation code GEANT4 and validate our use of it using published data, (4) Study, using GEANT4 and published data, the neutron production from and activation of MLCs made of different materials (e.g. tungsten, iron, and brass) to determine the optimal choice of material for patient and personnel safety, (5) Commence work on the requirements for the remote treatment planning capability needed once the proton facility is operational, and (6) Initial work on setting up a Web-based system to enroll patients into proton therapy clinical trials.

**Body**

Together, the Hospital of the University of Pennsylvania (HUP) and The Children's Hospital of Philadelphia (CHOP) are building the most advanced cancer treatment facility in the world. This will be a fully-integrated facility utilizing state-of-the-art imaging and conformal treatment techniques for both conventional x-ray therapy and proton beam therapy. The project involves close collaboration between the HUP and CHOP. HUP is planning to build its Center for Advanced Medicine (CAM) on a site directly adjacent to a new CHOP building, which will house a proton therapy facility. The CAM building is estimated to cost approximately $230M and a new HUP Radiation Oncology Department will be housed in one of the basement levels of this new building, where state-of-the–art conventional x-ray therapy and imaging equipment totaling approximately $20 M will be installed. This new Radiation Oncology Department will connect seamlessly at this underground level with the proton therapy facility in the new CHOP building. The proton therapy equipment will cost approximately $80–100M and the part of the CHOP building housing this equipment is estimated to cost a further $100M. In addition, HUP and the Walter Reed Army Medical Center (WRAMC) have formed a collaboration and have initiated research projects related to the new proton facility. The goal of the collaboration is to provide the technology, infrastructure and funding so proton therapy can reach its full potential of delivering the most conformal radiotherapy possible.

A project of this size and scope requires careful planning and equipment selection is a key issue. The original request for proposal (RFP) for supplying equipment was distributed to five major proton equipment vendors in March 2003. An important element of the RFP was that a single vendor should be responsible for supplying the proton therapy equipment, the imaging and conventional x ray therapy equipment. This vendor should also be responsible for connectivity issues. As no single vendor can supply all this equipment, this resulted in the formation of consortia, with one vendor taking responsibility for the whole project. There were four responses and a preliminary review of these proposals, followed by an external advisory committee meeting reduced the number of acceptable proposals to three. The three acceptable proposals were from IBA-Elekta, Hitachi-Varian and Siemens-Accel, (the first named vendor in each consortium taking overall responsibility for the project).

Some unexpected developments occurred and led to some delays with the vendor selection process. Specifically, Siemens broke their relationship with Accel and deciding to enter the particle therapy market offering a combined $^{12}C$/proton synchrotron. That decision led to a reappraisal of the proposals. In the summer of 2004 it was decided to issue a clarification of the RFP and to form a final vendor selection committee, comprised of HUP and CHOP personnel. The request for clarification of proposals (RFP-C) was distributed to Accel, Hitachi, IBA and Siemens in November 2004. After reassessment of these RFP-Cs the following consortia emerged as contenders for the final contact: Accel with Varian, Elekta or Siemens, IBA with Varian, Elekta or Siemens and Hitachi with Varian. During April and May members of the vendor selection committee made site visits to Hitachi in Japan, IBA in Belgium and Accel in Germany, to further refine technical specifications and enter into in-depth financial negotiations. At the present time the outcome of these negotiations is being analyzed and presented to the Board of Trustees of both CHOP and UPHS with final funding approval anticipated this summer and final vendor selection and contract signing in the fall 2005. The project is a complex and

expensive undertaking, one of the single largest projects undertaken by HUP and CHOP. It is, therefore, important that all those involved demonstrate that due diligence has been exercised in negotiations between HUP and CHOP and in the process of vendor selection. This process has proved to be more time consuming than at first expected but should reach conclusion in the later half of 2005.

The rationale for the overall proton project lays in the fact that proton beams offer highly significant advantages over x-rays in the sparing of normal tissues. This is due to the physical characteristics of the proton beam compared to x-rays. X-rays are electromagnetic waves that are highly penetrating, and will deliver dose throughout any volume of tissue irradiated, regardless of thickness. Thus x-rays always deliver substantial doses of irradiation both proximal and distal to the tumor volume. Furthermore, even for the most energetic x-ray beams available for practice, the depth at which the maximum dose of radiation is delivered ($D_{max}$) ranges from as little as 0.5 cm to a maximum of 3 cm depending on the energy utilized. Because a tumor is almost always located deeper than these ranges, a higher dose is invariably delivered to the normal tissues proximal to the tumor, and the tumor is always treated in the region of the beam where the energy deposition is falling off. To some extent this can be overcome by bringing in beams from multiple directions, centered on the tumor, allowing the dose to sum within the tumor volume. However, since the beam travels throughout the entire thickness of the body, all normal tissues from the entrance area to the exit of the beam will be affected.

Unlike with x-rays, the absorbed dose of a proton beam increases very gradually with increasing depth and then suddenly rises to a peak at the end of a proton range. This is known as the Bragg Peak (Fig. 1). A proton beam can be directed so that the Bragg Peak occurs precisely within the tumor volume, something that can almost never be done with x-rays. The dose around the tumor volume is much less than the tumor itself, thus sparing the normal tissue in this area. The dose immediately beyond the Bragg Peak of a proton beam is essentially zero which allows for the sparing of all normal tissues beyond the tumor volume. Side effects, both acute and long-term, typically seen with x-ray therapy can thus be markedly reduced with proton beams by sparing normal tissues that are situated around the tumor. These considerations are directly related to the physical characteristics of the proton beam, and require no demonstration or study. Initial clinical studies demonstrate the efficacy of proton therapy. It should be remembered however that the available clinical data are somewhat limited because most proton facilities have treated only a limited number of patients.

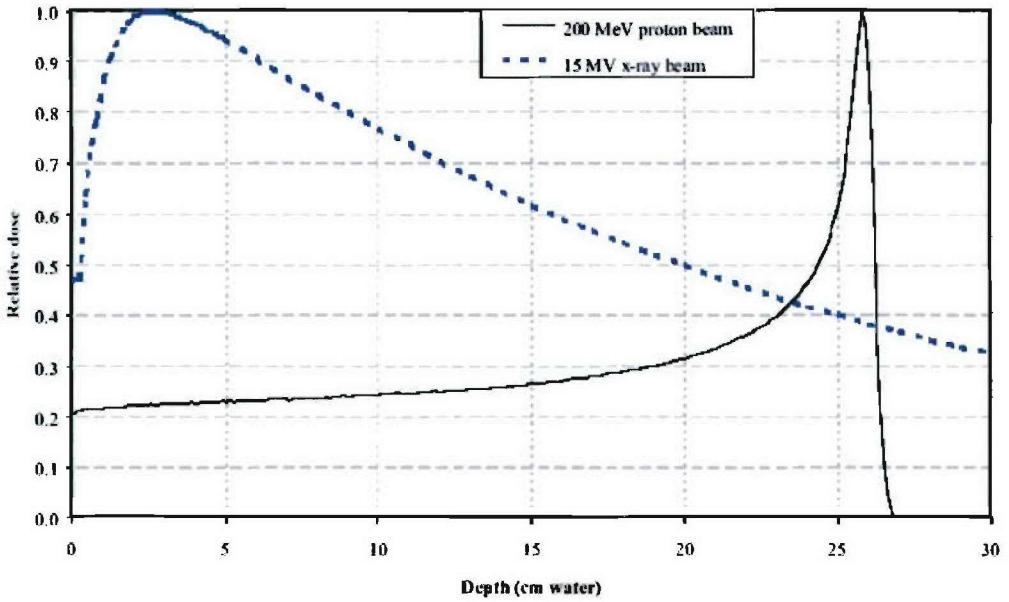


**Fig. 1.** Comparison of the relative depth dose for proton and x-ray beams.

A number of published studies[1-6] have documented the clinical advantages of proton beams, and shown decreased normal tissue toxicity, compared to conventional photons. Numerous sites within the body have been shown to be more effectively treated with proton beam therapy. By limiting the dose to normal structures, higher doses can safely be delivered to the tumor itself. This should result in higher local control and ultimately increased survival while minimizing side effects of therapy.

The treatment of pediatric tumors with proton therapy provides a unique opportunity to significantly reduce the acute and long-term complications associated with conventional radiation therapy. The pediatric population is exquisitely sensitive to the effects of radiation therapy. Long-term sequelae including growth abnormalities, second malignancies, neurologic complications, cardiac and pulmonary toxicities, and infertility may all be reduced with the use of proton therapy. X-ray therapy causes effects on the hearts and lungs of pediatric patients, again due to the problem of "exit" dose. A study of long-term survivors of children treated with x-rays to the spinal axis showed that 31% had abnormal EKGs and 75% had reduced exercise capacity. Jakacki et al.[7] reported that 60% of patients treated to the spine showed restrictive lung disease. Proton beams should be able to entirely avoid these complications since the uninvolved normal structures can be totally avoided.

The research element of the proton facility has brought together the expertise of HUP and WRMAC to initially identify five projects, to be started over a period of five years, that will result in the technology and protocols to make the new center the most advanced cancer

treatment facility in the world. Each of these projects will help advance proton therapy worldwide and result in measurable benefits. The five projects are as follows:

(1) Multi-leaf collimator (MLC) for use on proton therapy gantries
(2) Cone Beam CT on the Gantry for localization of target volumes
(3) Proton Radiography to determine dose and stopping power of various tissues
(4) Positron Emission Tomography (PET) imaging on the gantry to evaluate dose deposition within tissues irradiated
(5) Scanning proton beam using adaptive radiotherapy techniques based on implementation of MLC, Cone Beam CT, PET imaging.

This report concentrates on the first year achievements of the multileaf collimator design and development project. This is the first of the five proposed projects to be approved and funded. The overall project is running approximately 4-6 months behind schedule. Most of this delay is attributable to the time it took to recruit staff. The second year of the proposal calls for working directly with the proton therapy equipment vendor to develop a multileaf collimator prototype. If the vendor is selected in the fall of 2005 as projected no additional delays are anticipated.

The Statement of Work in the approved grant proposal included the following items to be investigated during the first year:

1. Leaf design: The specification of the leaf material and shape will be determined so the final design will: (1) reduce to permitted levels the leakage of radiation through the MLC onto the patient; and (2) keep the activation of the MLC, and consequently the exposure to our radiation workers, to as low a level as can reasonably be achieved. This work will be performed in consultation with our chosen vendor using a combination of published literature and Monte Carlo simulations.

2. Joint Military/Civilian Proton Radiotherapy Center: The oversight and management for this research will be coordinated through a Joint Military and Civilian Proton Radiotherapy Center to be established at Walter Reed Army Medical Center. Approximately 5% of the total funding will be necessary for renovation of space at WRAMC to create this center. This center is necessary to provide working space for the project administrator and scientific writer. This Center will also serve as the hub through which the Walter Reed investigators will conduct their research on this proposal. In addition to the oversight and management to be provided through this center and the research performed by the Walter Reed investigators in this Center, a third purpose of this center will be life cycle management of the Center in order to secure continual funding to guarantee this Center is transformed into the remote treatment planning and management clinic envisioned in the preface [of the grant proposal].

3. Investigate the design factors affecting the lateral penumbra of the beam: The quality of the dose distribution from a proton beam, particularly the lateral penumbra, directly depends on the distance between the final collimator and the patient surface. Ideally we want the MLC as close as possible, but that may limit the ability to rotate the gantry around the patient. A compromise solution will be determined using Monte Carlo simulation to study the effect the position of the MLC has on the lateral penumbra.

4. Design of the MLC system: The electromechanical design and assembly of the MLC will be done in consultation with the chosen vendor. The leaf drive mechanism must be designed to minimize the overall dimensions of the collimator. A high-precision leaf position setting and verification system must be designed. The mechanism for mounting the collimator assembly on the proton beam delivery nozzle must be designed to avoid patient-collimator interference problems and be adaptable to the specific requirements for treating a wide range of anatomical sites. A suitable computer-based control system will be designed, which will allow for the treatment of individual fields as a series of multiple segments. We expect to take advantage of the experience gained from the manufacturers of x-ray MLCs.

In addition to the Statement of Work there was one major activity during the first year, which was to assemble the additional personnel both at HUP and at WRAMC as described below.

A. Personnel at HUP and WRAMC

Four new positions were approved in the grant proposal to facilitate the completion of the research. Two of these positions were at HUP – a postdoctoral fellow and a student. The postdoctoral fellow position was advertised in Physics Today, which is the monthly trade magazine for physicists. More than sixty applicants were reviewed and Dickson Goulart, PhD was hired and started in November 2004. Dr. Goulart has spent all of his time installing and running the GEANT4 simulation code on the PCs purchased for that purpose.

At Walter Reed an Executive Director (Gary Ashton, PhD) and a Radiation Physicist (Dan Fry, PhD) were hired in 2005. Dr. Ashton coordinates the project on the Walter Reed side and interfaces with the administration at HUP. Dr. Fry is involved with the HUP physicists working on the simulation program and has joined with them on several visits to existing proton facilities.

The Walter Reed Army Medical Center Space Committee approved the first phase of renovation of space to accommodate the above staff. Contracts have been awarded for renovation and the completion date is expected to be at the end of June 2005. The second phase of the space renovation is on-hold subject to a consideration of the implications of the DoD BRAC announcement.

B. Remote Treatment Planning

One of the goals of this project is to establish a joint HUP/WRAMC proton radiotherapy center to facilitate both patient treatment planning and further research. This Center will serve as the hub through which the Walter Reed investigators will conduct research on this proposal aimed at developing generic remote treatment planning and comprehensive quality assurance systems not only for the collaboration with UPENN but to underpin DoD interests in this area more generally. Research performed to date includes validation of simulation tools needed for quality assurance of clinical dose estimates. The transport media modeled is being progressively modified from homogeneous soft tissue equivalent phantoms to inhomogeneous media that will be representative of the spatial and temporal complexity required for treatment planning with patients. The strategic

focus of the research is to inform the Center of the appropriate planning tools, methods and validation strategies needed to support the development of high quality remote clinical treatment plans. It is expected the complexity of this task will evolve as proton beam facilities increasingly attempt to integrate and adopt a variety of treatment delivery modalities and fuse data from advanced imaging techniques

A group from HUP visited Walter Reed to learn about their TELESYNERGY® system that was installed in the WRAMC Radiation Oncology department. This remote medical consultation workstation was developed through the National Cancer Institute and has been installed in approximately twenty locations in the United States and in four other countries. It is a very efficient way to remotely view a variety of patient image studies and seems to be a natural way for staff at WRAMC and at the proton facility to communicate.

As a first step in this direction, HUP has installed a Tandberg 880 MPX that permits HUP and WRAMC to interact over an ISDN line capable of transmitting over 800 kilobytes per second. The immediate effect that this had was to allow the staff at the two institutions to more easily participate in the research work being performed at the other institution. We expect that this system will expand into a way for staff at the WRAMC to fully participate in the planning of their patients who are treated at the proton facility.

In addition to the hardware installed at HUP, a joint HUP/WRAMC Clinical Task Force has been formed to start the requirements-definition and process-mapping needed to plan a pilot remote treatment planning and delivery system. This work will identify the risks and management implementation issues and define the technology to be employed for a pilot trial using conventional photon treatments as a baseline for validation.

C. MLC design work using GEANT4 – validation

Much of the year-1 MLC design work specified in the Statement of Work used the GEANT4 Monte Carlo simulation program.[8] (The acronym GEANT came from "GEometry ANd Tracking"). GEANT4 is a software toolkit that was developed for high-energy physics by a world-wide collaboration based at CERN (Conseil European pour la Recherché Nucleaire), which is headquartered in Geneva, Switzerland. GEANT4 was the first development in high-energy physics to apply software engineering methodologies and object-oriented technology to a product. Because of the flexible software structure and extensive library of interaction data and models, it has also been successfully applied to space physics and medical physics.

As indicated in Fig. 2, the GEANT4 structure is modular; i.e., different parts of the software independently perform different functions. For example, the geometry of the simulation is constructed separately from the selection of the physical interactions that will be considered. The overall effect of the modularity is that different parts of the program provide specific functionality and can be refined independently. In addition to the modules provided by default, we merged ROOT functionality directly with the GEANT4 source code. ROOT is a powerful data acquisition and analysis toolkit developed by CERN which is widely used by the HEP community. This step added a

time-saving component to our framework in that a simulation can be run a single time but analyzed or visualized multiple times without repeating the entire simulation.

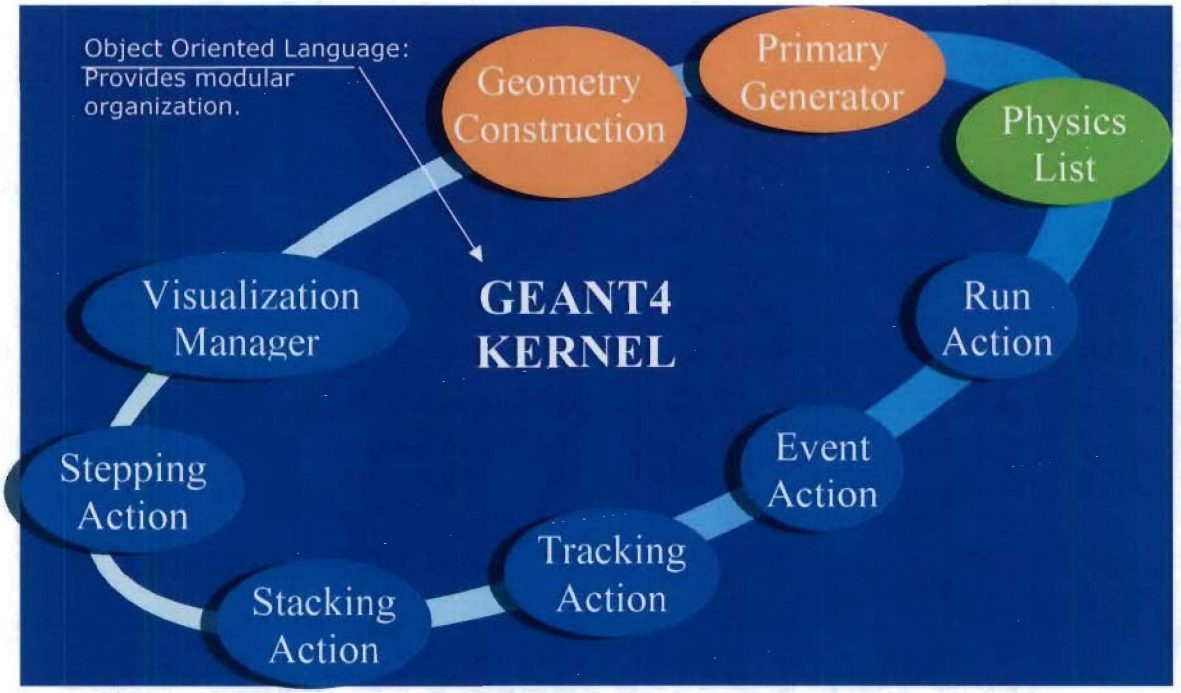


Figure 2: GEANT4 modular structure simplifies application to specific cases.

The toolkit contains extensive models and, in some cases, cross-sectional data that can be used to select which physical interactions will be considered during the simulation. For each type of interaction (hadronic or electromagnetic) the user can specify a lower energy limit below which particles will no longer be tracked. The user may also specify what secondary particles are of interest so that time can be used most effectively.

Before using GEANT4 to aid in our design of the MLC we first validated that the results it generated were consistent with experimental data or, in some cases, with data generated from other validated Monte Carlo programs. Figure 3 shows the dose deposited in a water phantom for 200 MeV proton beams, one a pencil beam and the other a 6 cm long × 6 cm wide beam. For the pencil beam the range was determined by integrating all of the dose at given depth; for the broad beam the range was determined by the dose deposited along the central axis. An example of the depth-dose distribution from these simulations is shown in Fig. 4.

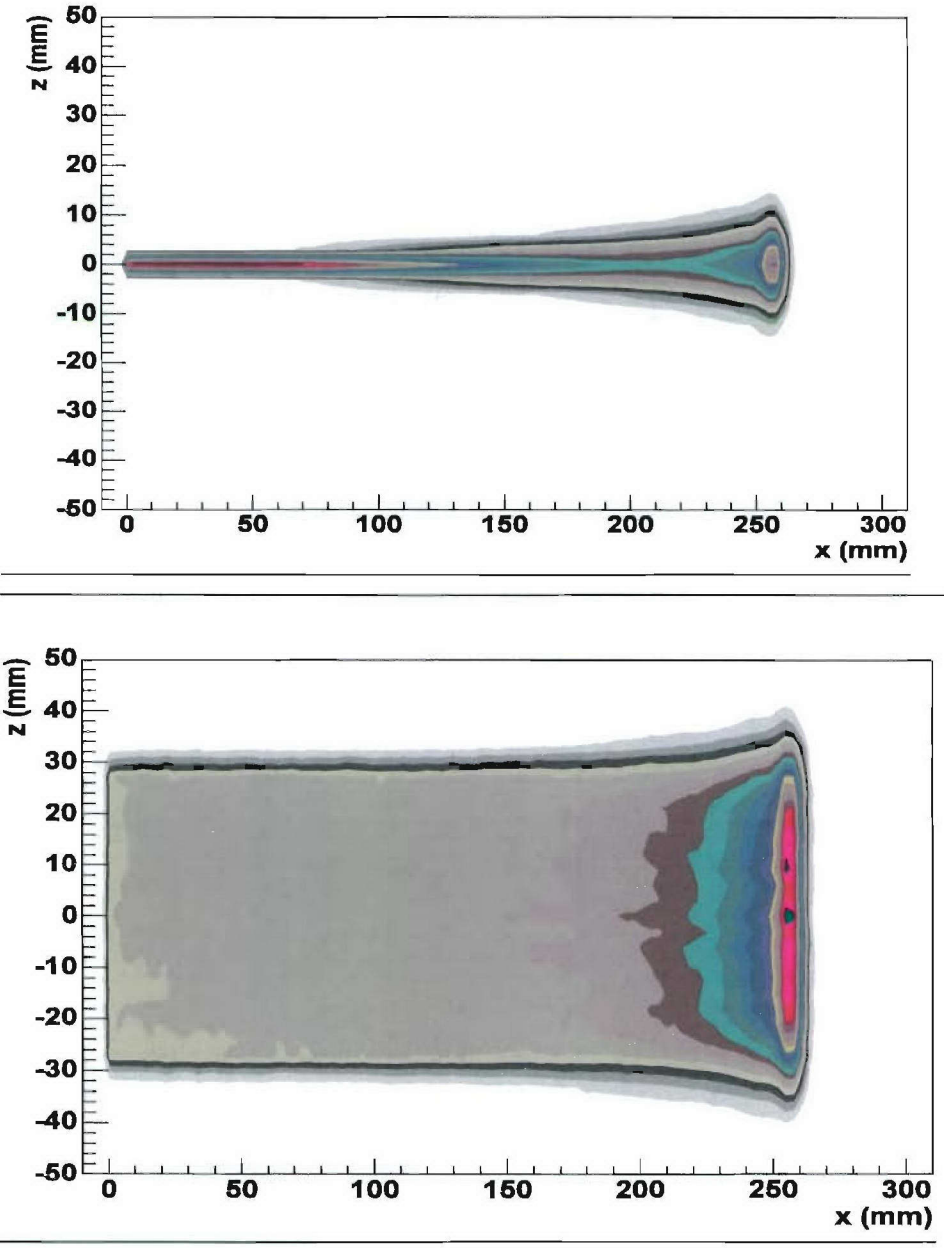


Fig. 3: Energy deposition in water by a 200 MeV pencil proton beam (top) and by a 6 cm × 6 cm field of the same energy (bottom).

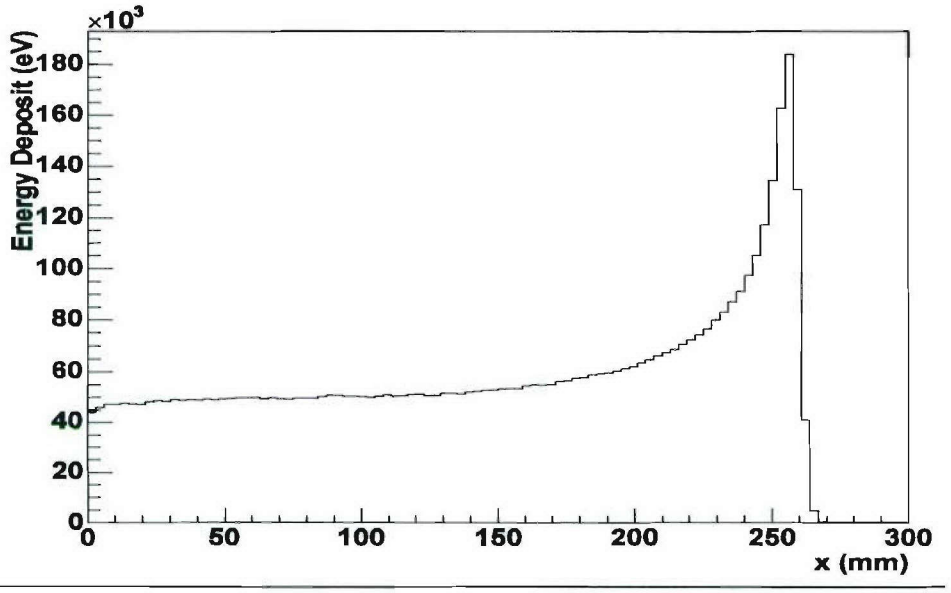


Fig. 4: Pristine Bragg peak for 200 MeV proton beam incident in water derived by integration of the energy deposited at depth by the pencil beam in Fig. 3.

The proton range was extracted from the depth dose distributions (Fig. 5) obtained from the Monte Carlo simulation and were compared to the ICRU range for four different proton beam energies 50 MeV, 100 MeV, 150 MeV and 200 MeV. The ranges were within 1 mm of the published ranges of 2.2 cm, 7.7 cm, 15.8 cm, and 26.0 cm respectively.[9] In addition the entire dose deposition curve was compared to Monte Carlo data for a 120 MeV proton beam that was validated with data obtained at the NPTC at the Massachusetts General Hospital in Boston (MGH).[10] An example of this comparison is shown in Fig. 6.

The validation data above show that the simulation properly calculates the energy deposited in the direction of the incident beam. We also validated the lateral distribution of the beam since it will be critical in our later work to design the MLC in a way that the lateral penumbra is minimized. To do this we simulated the beamline at the Orsay proton therapy center (CPO) outside of Paris. The elements in the beamline (Fig. 7) included scattering foils, modulator wheels, and ionization chambers. The penumbra was extracted from the profiles at different depths and compared to the data published by the Orsay group.[11] The upper plot in Fig. 8 shows the comparison of the data points calculated with GEANT4 and the result of the fit published in ref. 11. In that publication the penumbra and the depth were both expressed as "scaled"; i.e., each value was divided by the maximum for that parameter. The lower plot of Fig. 8 shows the true lateral penumbra (80% - 20%) in mm.

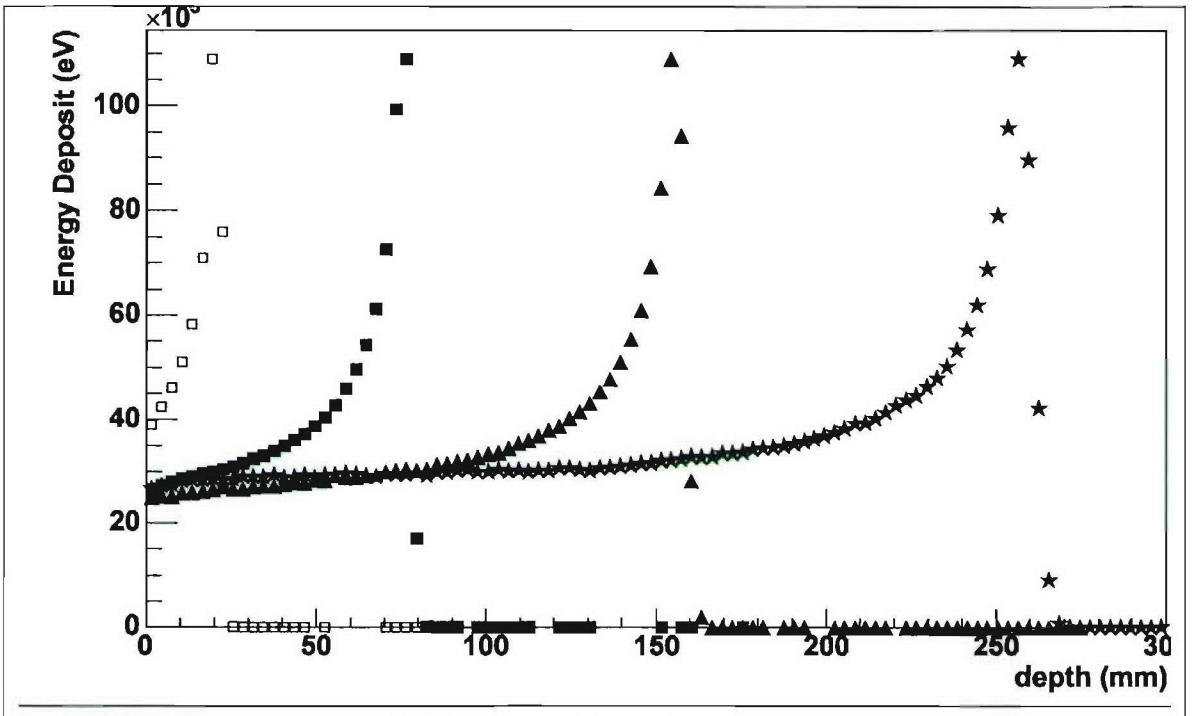


Figure 5: Energy deposition for four different proton beam energies showing respective pristine Bragg peaks (open square: 50 MeV, solid square: 100 MeV, triangle: 150 MeV and star: 200 MeV).

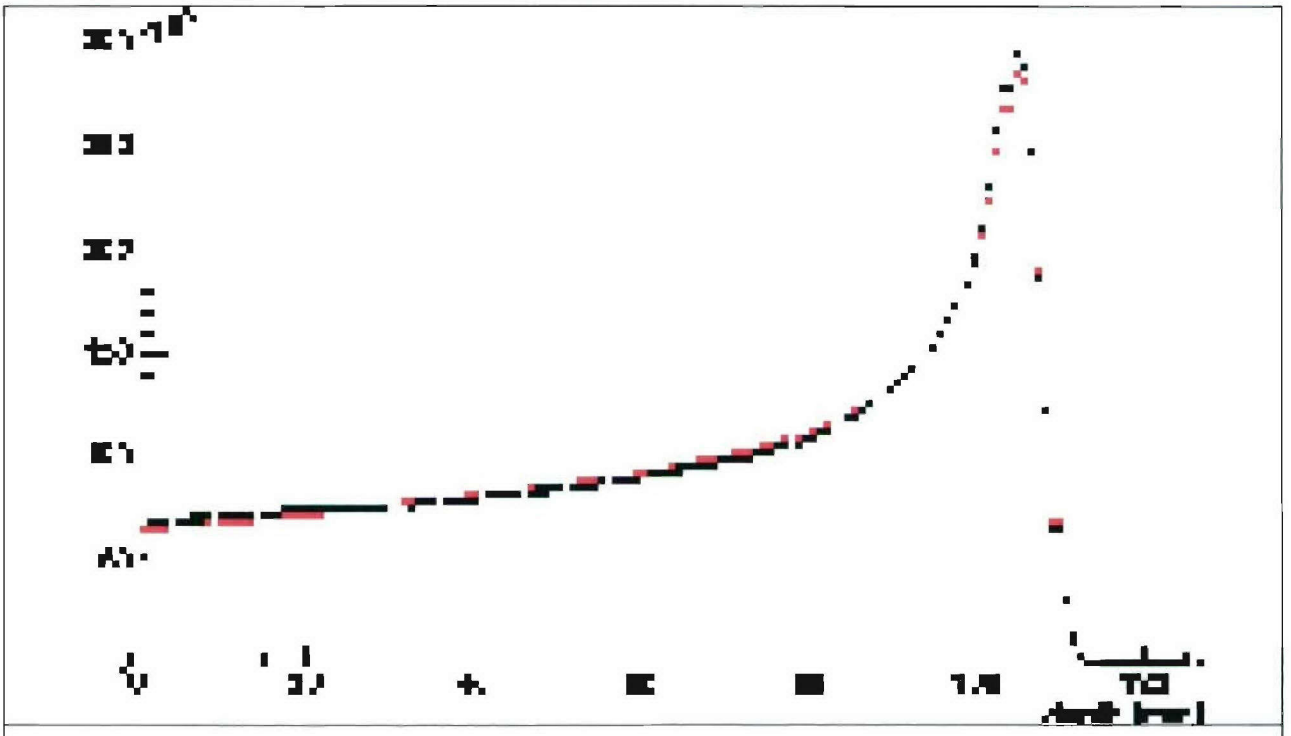

Fig. 6: Comparison between HUP data (black) and MGH data (red) for a 120 MeV proton beam.

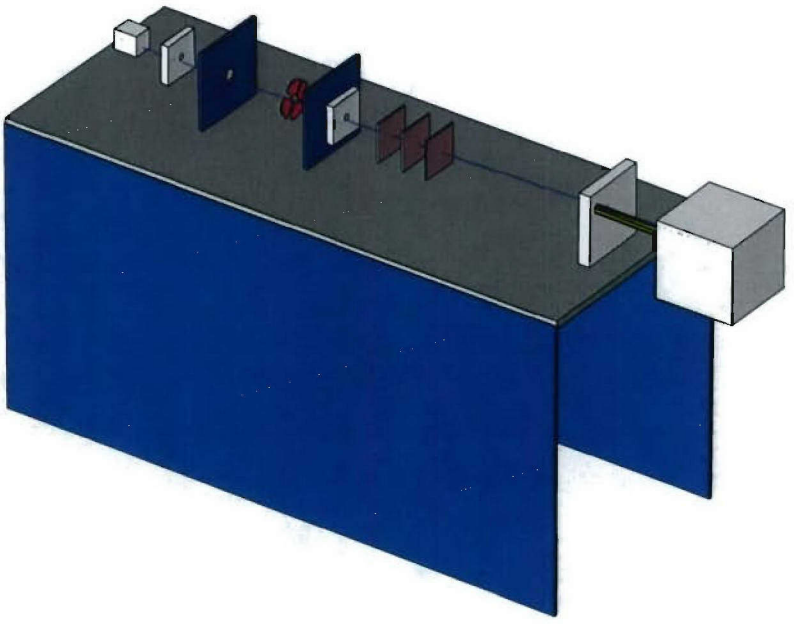

Fig. 7. GEANT4 simulation of the proton beam in Orsay that was used to validate the multiple scattering model.

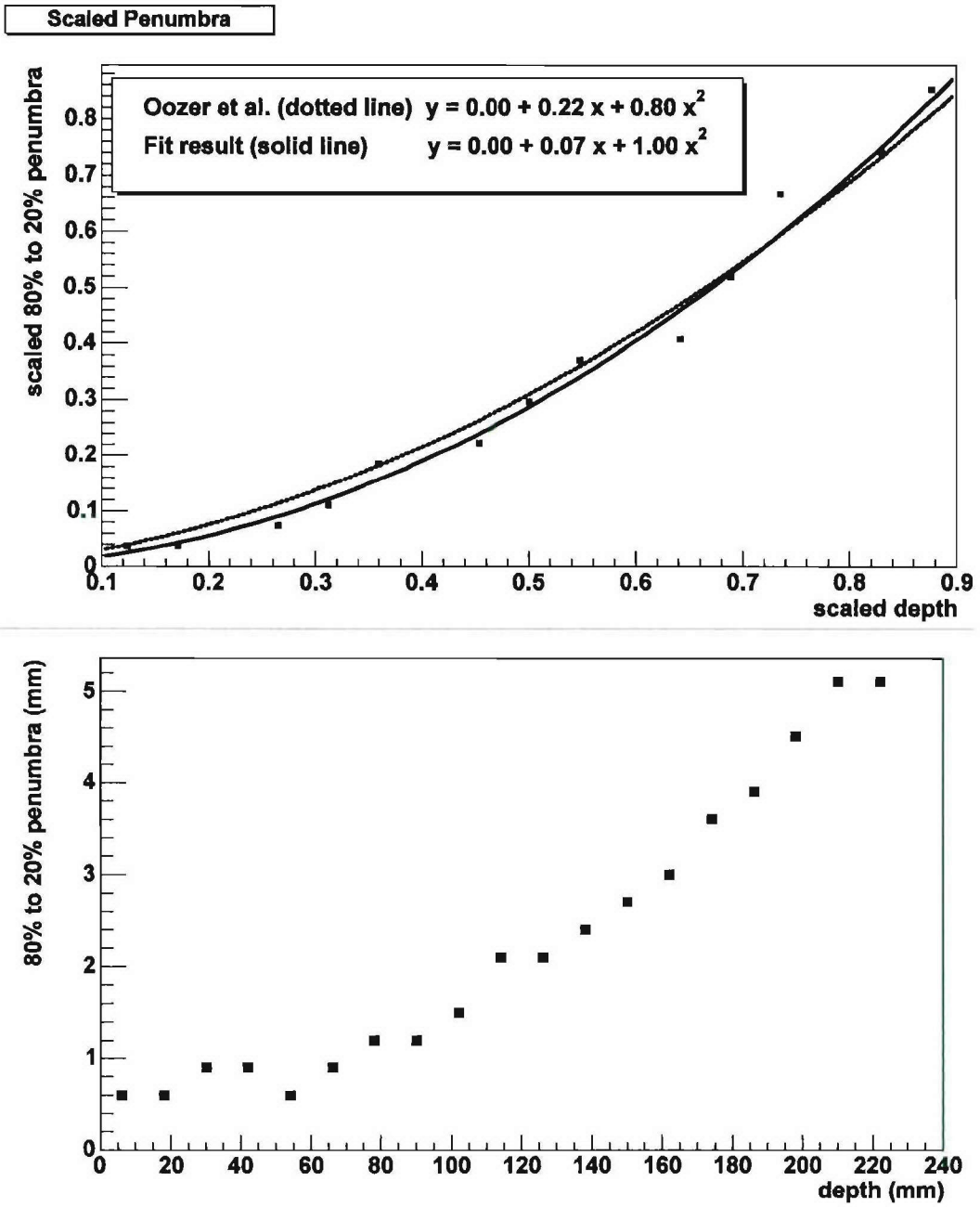


Figure 8: Penumbra due to multiple scattering is consistent with models based on experimental data.

After validating that GEANT4 was accurately transporting proton beams, the two next steps were to incorporate the MLCs into the simulation geometry and to look at radiation safety concerns related to neutron production and leakage. In determining the parameters of the MLC we investigated existing designs presently in use at other facilities. Compared with the MLC at the Heavy Ion Medical Accelerator in Chiba[12] (HIMAC) and the Hyogo Ion Beam Center our initial designs are similar (Fig. 9). The leaves of the multileaf collimator (MLC) have a rectangular cross section and move in non-diverging path. The MLC is made up of two opposing banks of 40 pairs of 10 cm thick, 65 mm in long and 5.0 mm wide tungsten leaves.

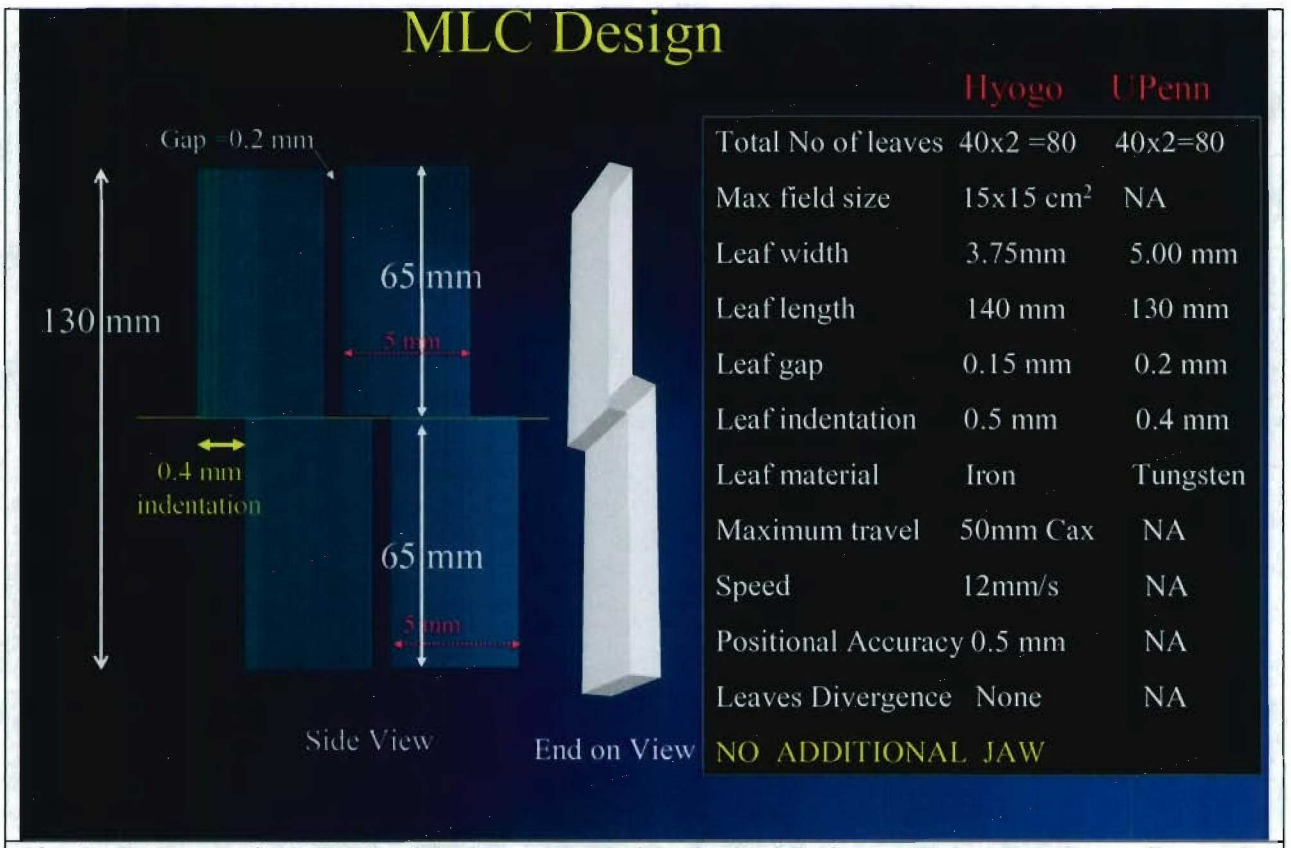


Fig. 9: One potential MLC leaf design compared to the leaf design at Hyogo Ion Beam Center. In the side view the beam enters from above.

We varied the leaf thickness between 0.5 and 1 cm (Fig. 10). The smaller leaf thickness conforms to the desired shape better then the larger leaf thickness. Also, in considering the development of a prototype, most manufactures commonly use either 0.5 or 1 cm leaves so development time may be reduced.

For the leaf edge there were two designs incorporated in the Monte Carlo; one was a rounded edge and the other was a flat interlocking edge (Fig. 11). For treatment linacs curvature of the leaves are determined to minimize the variation in the penumbra off the central axis due to changing absorption.[13] For proton beams scattering and leakage rather than attenuation will be

the issue for designing the leaf edge. The consequence of introducing rounded edges for proton beams is when the leaves outside the field are closed the junction between them isn't thick enough to stop particles inside the collimator, increasing the leakage through the collimator. Figure 12 shows the result of initial leakage studies for the flat edged leaves. With all the leaves closed the primary protons are stopped inside the MLC.

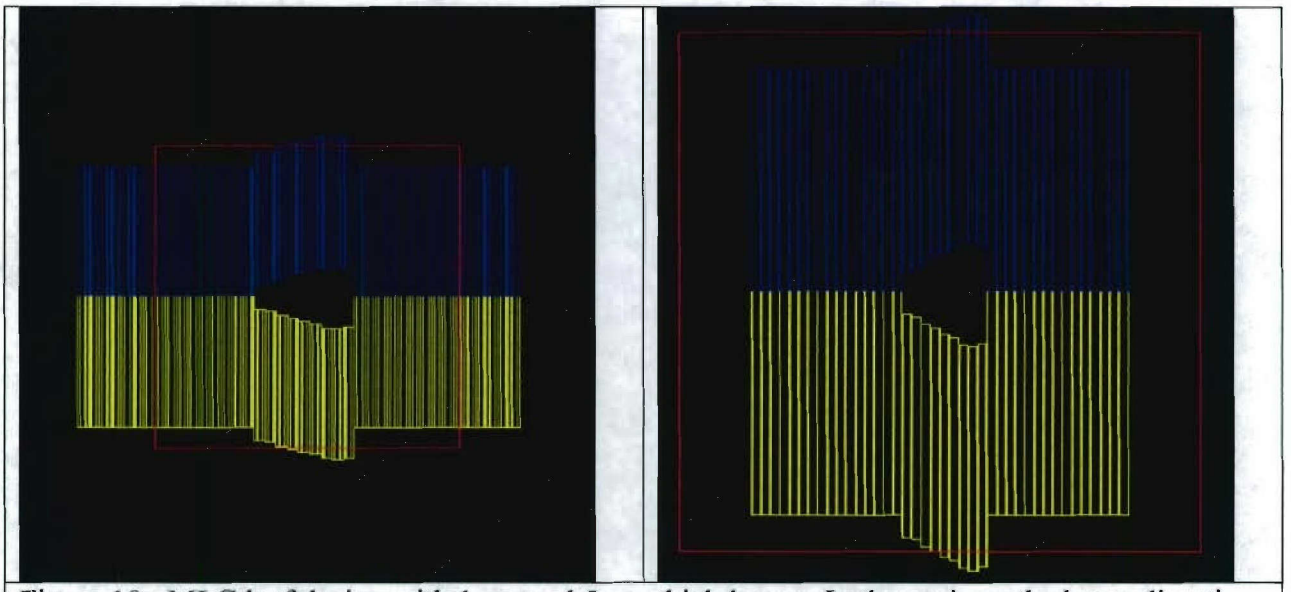

Figure 10: MLC leaf design with 1 cm and 5mm thick leaves. In these views the beam direction is into the page.

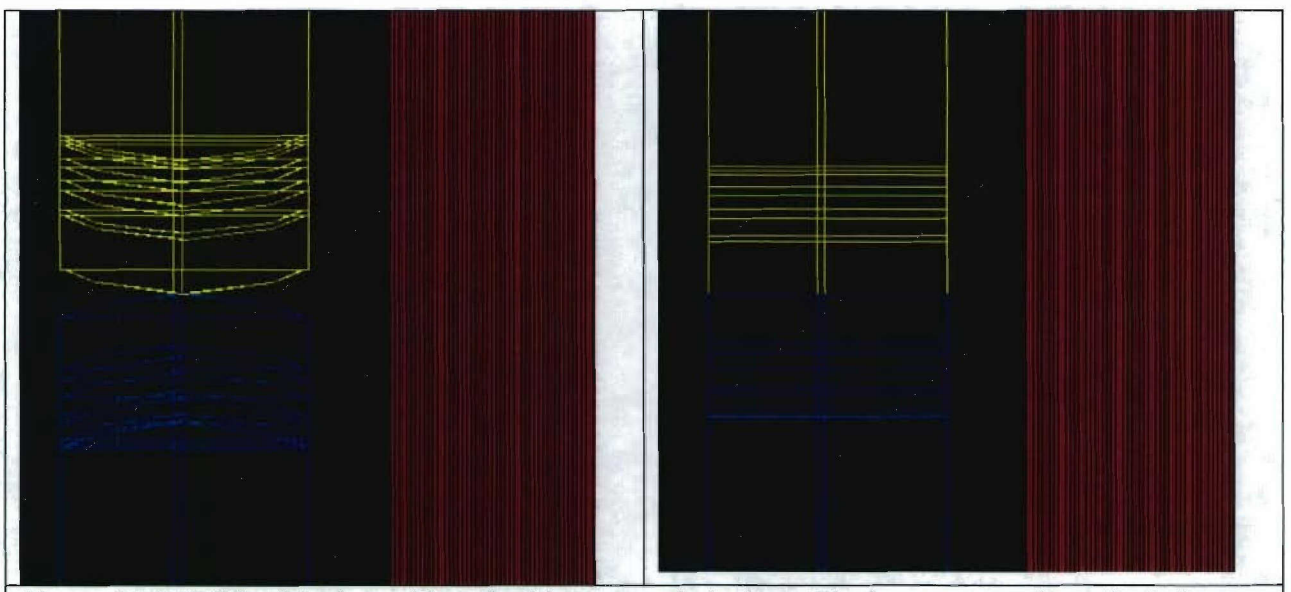

Figure 11: MLC leaf design with and without rounded edges. The beam enters from the left; on the right of the MLC is part of the water phantom. The leaves move in the up/down direction.

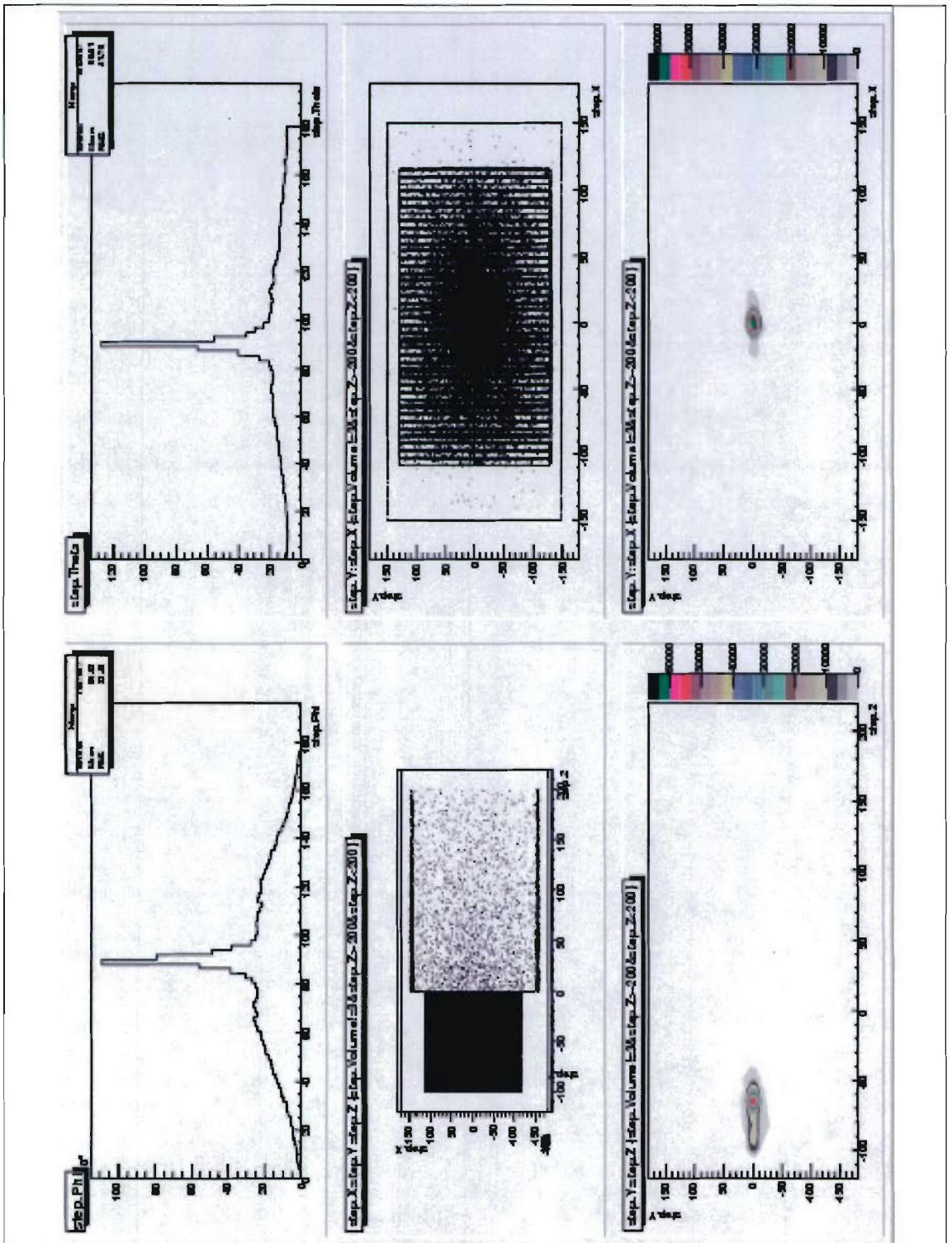

Figure 12: TOP – Theta and Phi distribution for all particles in the MLC and water phantom.
MIDDLE – Side and Beam's eye view of MLC and water phantom.
BOTTOM – Initial leakage studies of MLC.

In addition to leakage through the leaf edges, leakage between the leaves can be a problem. MLC leaves are machined to a high degree of precision but, because a small gap must be left between the leaves to allow for movement, particles can still find their way through the MLC and to the patient. To remedy the situation leaves can be designed to absorb particles that travel in the gaps by adding a stepped edge.[14] Figure 13 illustrates different designs for stepped edges. We have implemented the single step design into the Monte Carlo, gaps between the leaves are kept within 0.2 mm with a step size of 0.4 mm.

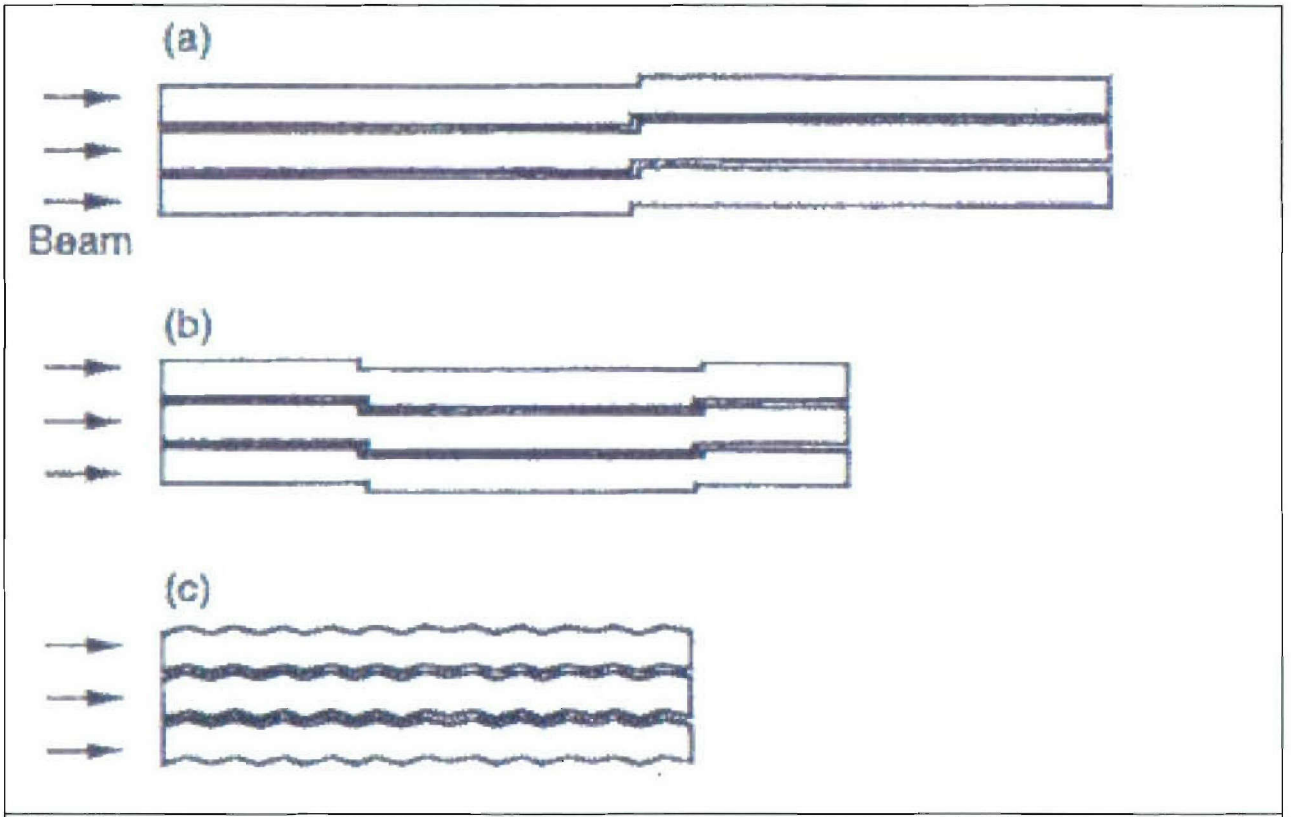


Figure 13: Three potential MLC leaf designs used to study leaf leakage; (a) single step, (b) double step, and (c) corrugated. The beam enters from the left and the leaf movement is in and out of the page in these views.

D. Neutron production and MLC activation

The design of a multi-leaf collimator for a proton therapy facility includes consideration of leaf thickness and the neutrons and radioactive products generated by proton interactions in the collimator material. The range of protons decreases with increasing density of the leaf material, which suggests fabricating the MLC with a high density material such as iron, brass or tungsten. However, the induced radioactive activity depends on the material used to fabricate the MLC as does the rate of proton induced neutron production. In this work we used both Monte Carlo simulations and published

data to understand the neutron production rate and radioactivity induced by high energy protons in these potential materials for fabricating a proton MLC.

**Neutron Production**

Initial MLC runs were performed using the GEANT4 Monte-Carlo code. The rate of neutron production and the neutron energy spectra produced by the absorption of protons with different energies in iron, brass and tungsten was evaluated. The simulated leaf had a cross-sectional area of 1 $cm^2$ and 10 cm in length. Figure 14 show the relative neutron flux in the different leaf materials. For comparison, the figure also shows the simulated neutron flux generated in water. The figure demonstrates both that the neutron production increases with atomic number and proton beam energy.

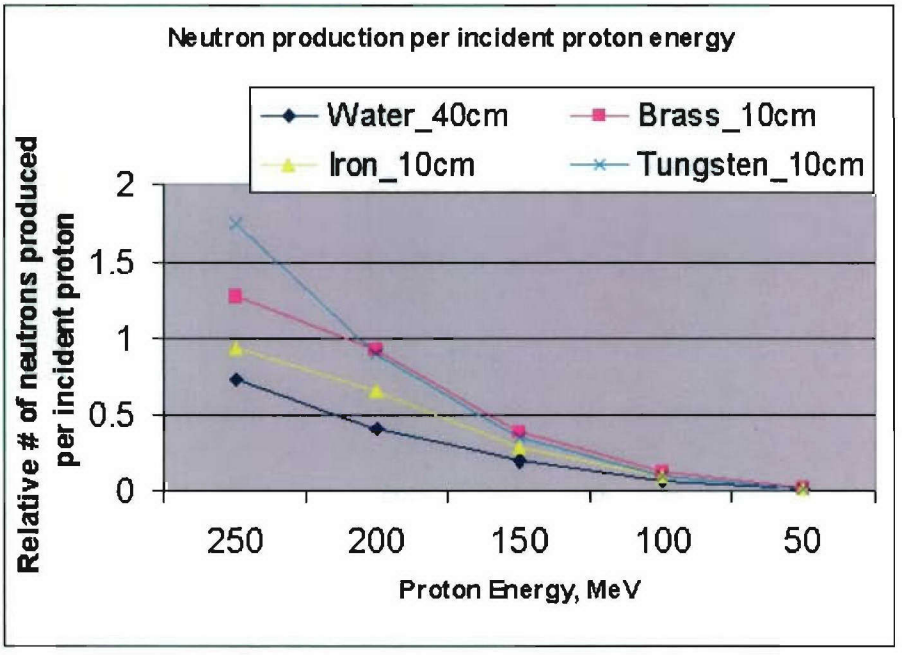


Fig14. Relative neutron production per incident 250 MeV protons on a leaf 1 $cm^2$ in cross-sectional area and 10 cm in length in iron, brass, and tungsten

The distribution of the neutron energies produced by the absorption of protons with energy of 250 MeV is shown figures 15a, 16a, and 17a for brass, iron and tungsten respectively. The cumulative distributions Figures 15b, 16b and 17b indicates that 95% of the neutrons produced have energy less than 60 MeV in the three materials.

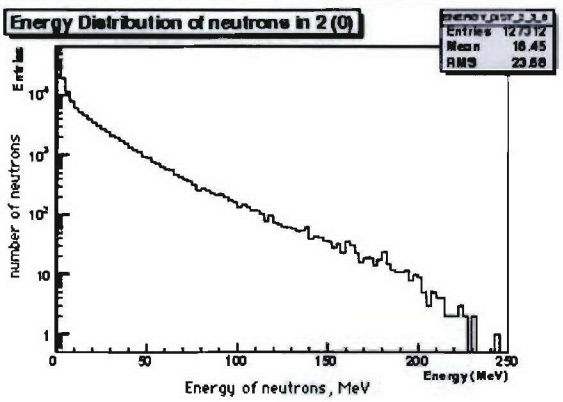


Fig 15a. Neutron energy spectra in brass, 10cm, 250 MeV protons

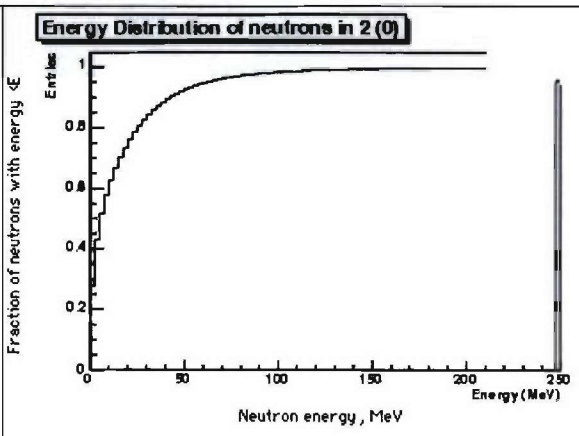


Fig 15b. Cumulative neutron energy spectra in brass,10cm, 250 MeV protons

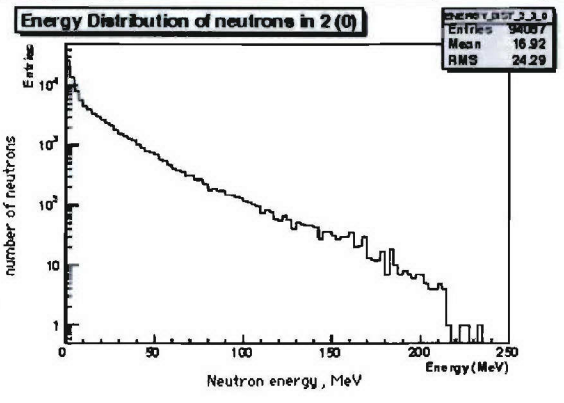


Fig. 16a. Neutron energy spectra in Fe, 10cm, 250 MeV protons

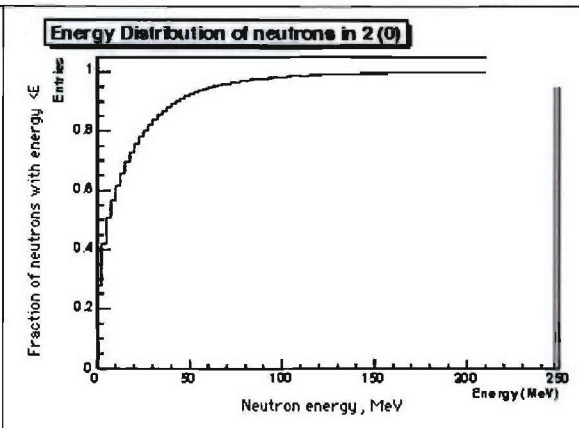


Fig. 16b Cumulative neutron energy spectra in Fe, 10cm, 250 MeV protons

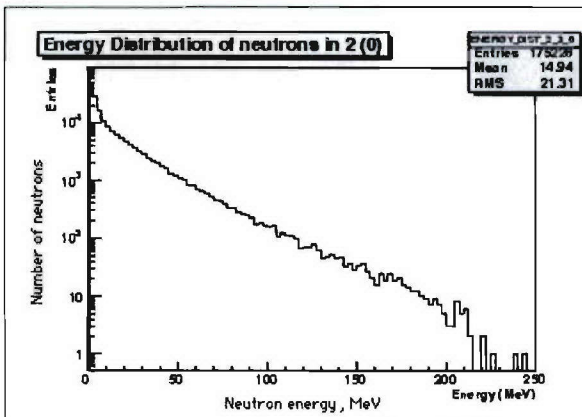


Fig.17a. Neutron energy spectra in W, 10cm, 250 MeV protons

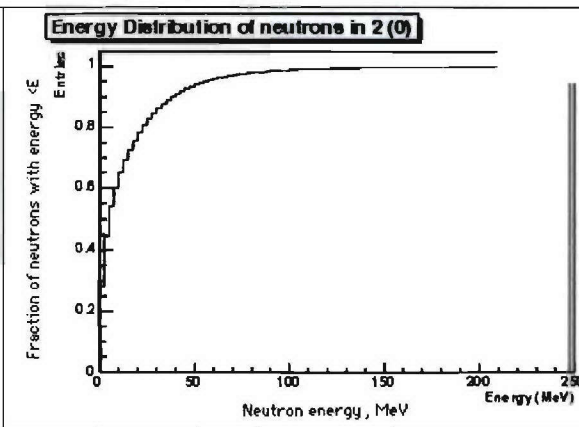


Fig.17b. Cumulative neutron energy spectra in W, 10cm, 250 MeV protons

**Nuclear spallation events in different MLC materials.**

The rate of nuclear spallation events whereby particles such as n, $H^2$, $H^3$ and $\alpha$ are ejected due to proton interactions depends on the target nucleus. The GEANT4 Monte-Code code was used to determine for incident protons having an energy of 250 MeV the rate of these reactions in tungsten and iron. For these simulations a slab of material having a thickness corresponding to the range +1 cm for 250 MeV protons in the materials was studied. The cross-sectional area of the proton beam was 5 x 5 $cm^2$ Table 1 shows the rate of production of neutrons, deuterons, tritons, and alpha particles in the two materials. The data demonstrates the increase in neutron production with atomic number. The rate of production of deuterons, tritons and alpha is nearly the same in the two materials. The secondary dose to the patient due to this neutron flux is under investigation. The rate of neutron production derived from Monte-Carlo simulation was compared with published cross-section data.

**Table 1**

**Number of n, $H^2$, $H^3$ and $\alpha$ Produced in Iron (Fe) and Tungsten (W) per absorbed 250 MeV proton**

| | # of neutrons | # of deuterons | # of tritons | # of alphas |
|---|---|---|---|---|
| Iron MLC Thickness =8 cm | 2.2 | 0.13 | $6.5 \times 10^{-2}$ | 0.12 |
| Tungsten MLC Thickness =5 cm | 8.0 | 0.13 | $6.9 \times 10^{-2}$ | 0.10 |

**Neutron production evaluated using measured cross-section data**

Published[16] and unpublished[17] cross-section data was used to evaluate neutrons produced in iron, brass and tungsten as a function of proton energy. Cross-section data (EXFOR/CSISRS) and (Iljinov et al, 1992)[18] for the following 5 proton induced neutron reactions were used to obtain reliable neutron yields: (p,n), (p,2n), (p,pn), (p,p2n) and (p,n$\alpha$). Other reactions were reported in a (p,x) format which allows only an approximation for estimating the induced neutron yield. The lower limit for the neutron production derived from this analysis was 1-2 neutrons per absorbed 250 MeV proton independent of material. The neutron yield obtained from the Monte-Carlo simulations 2.2 and 8 (see table 1) is significantly higher. Because of the uncertainties in the published experimental data for the (p,x) reactions the Monte-Carlo results will be used to determine the neutron production in the multi-leaf collimator material. A benefit of the Monte Carlo is that it enables us to get dose distributions in addition to the number of secondaries produced. Figure 18 (top) shows the energy deposited in water by a 250 MeV 5 x 5 $cm^2$ proton beam. The bottom of figure 18 shows the neutron dose component produced by the same proton beam. These figures show (1) the neutron dose is at least 1000 smaller than the proton dose, and (2) whereas the proton dose component is limited to the irradiated field, the scattered neutrons contribute dose outside the irradiated fields.

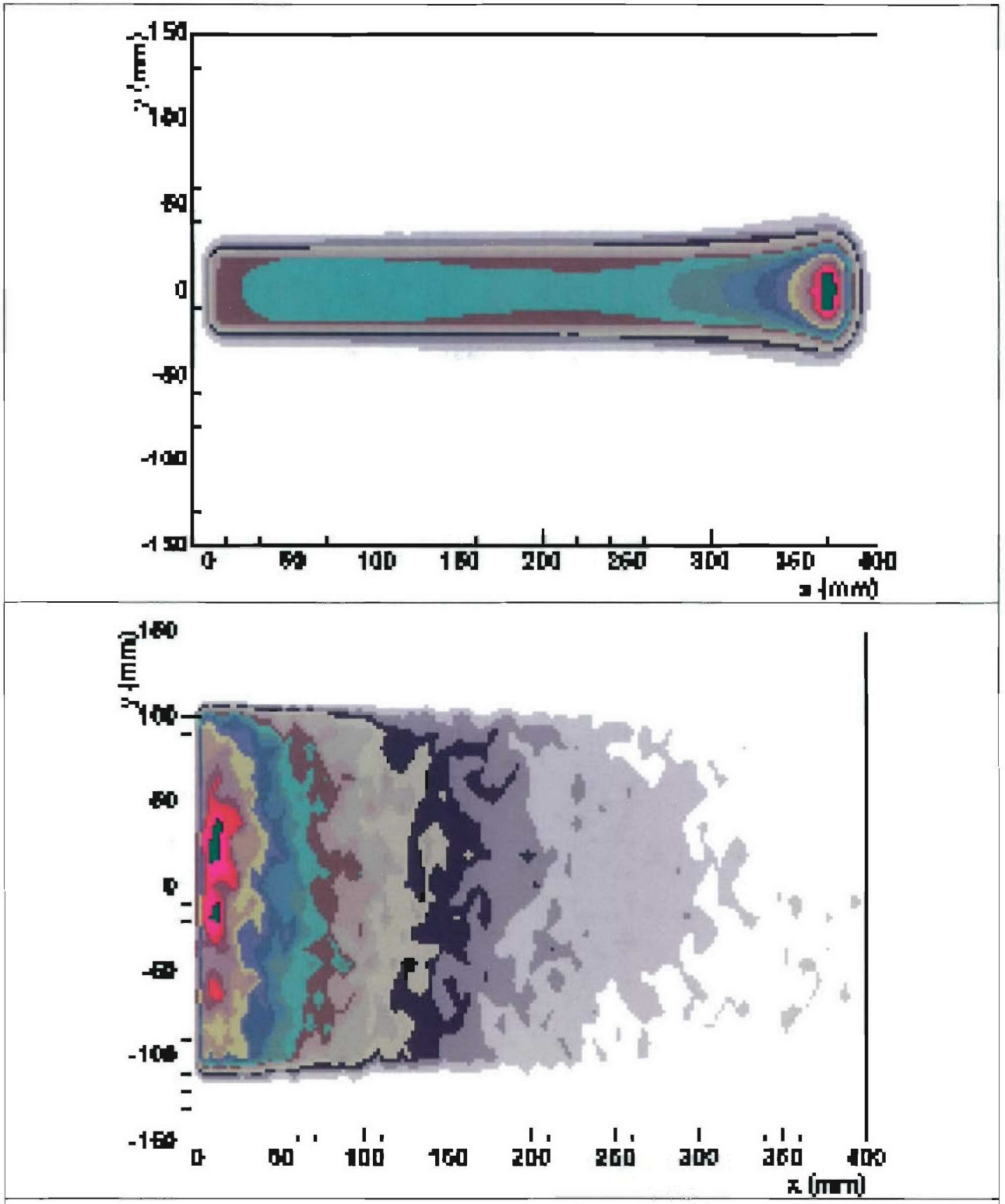


Fig. 18. Relative dose distributions in a water phantom from proton beam (top) and from secondaries produced in a collimator just in front of the phantom (lower). The display is scaled so a color in the upper plot corresponds to a dose ~1000 times higher than in the lower plot.

**Induced radioactive gamma emitting isotopes derived from published cross-section data**

The same cross-section data was used to estimate the gamma activity produced in iron and tungsten due to the absorption of 250 MeV protons. Due to self-absorption of low energy gamma rays in the simulated leaf material only gamma rays with energy above 0.45 and 0.2 MeV in tungsten and iron respectively were included when evaluating the generated gamma activity. Figure 19a and 19b shows the gamma activity as a function of time induced by the absorption of $10^{14}$ 250 MeV protons in tungsten and iron respectively. The rapid decay in activity in tungsten is associated with the production of the short-lived isotopes and the long decay with gamma emitting isotopes with half-lives >1 week. The initial activity is significantly greater in iron than in tungsten, however after 1 hour the activity in both materials is approximately the same. The calculated activity of isotopes produced in brass was found to be of the same order of magnitude as the experimental measurements by J. Sisterson (2002).[19] The gamma ray activity in brass was found to be approximately twice that produced in iron or steel.

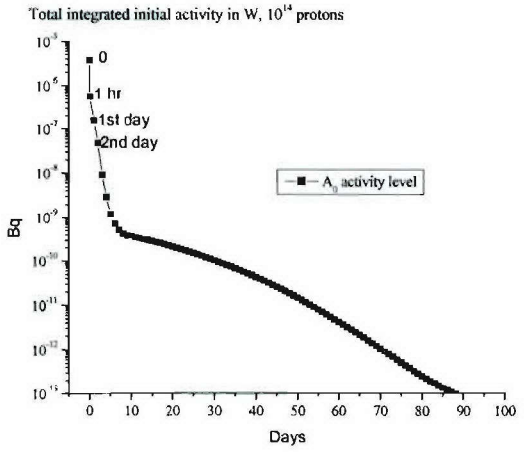


Fig.19a Total integrated gamma ray activity in a tungsten MLC, $10^{14}$ 250MeV protons

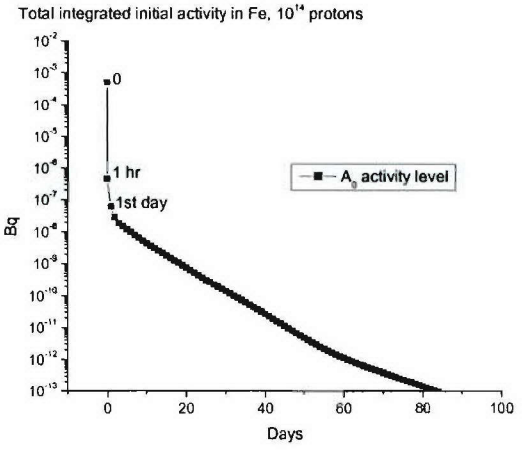


Fig.19b Total integrated gamma ray activity in an iron MLC, $10^{14}$ 250 MeV protons

The build-up of activity for daily treatments involving $10^{14}$ protons per day are shown in figures 20a and 20b in tungsten and iron respectively. The figures demonstrate that the maximum gamma activity is reached in less than 1 week in tungsten and approximately 3 weeks in iron. Knowledge of the induced gamma ray energies[20, 21] and activities in the leaf material was used to estimate the exposure at 10 cm from the leaf. In calculating the attenuation of gamma rays it was assumed that the gamma rays were at a single energy of 1 MeV from tungsten and 0.511 and 1.25 MeV for iron. For calculating the beam attenuation in the leaf material a thickness of 8 cm was used for tungsten and 14 cm for iron. Figures 21a and 21b are the calculated exposure at 10 cm from the leaf. These figures indicate that the exposure rate 10 cm from the MLC material will be less than

0.023 and 0.0026 mrem/hr from iron and tungsten respectively. Steel trace elements were found to be unimportant contributors to the gamma dose.

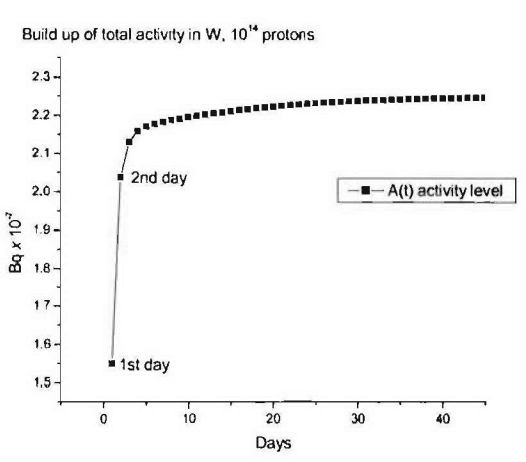


Fig. 20a. Build up of total gamma ray activity in a tungsten MLC; $10^{14}$ 250 MeV protons delivered daily

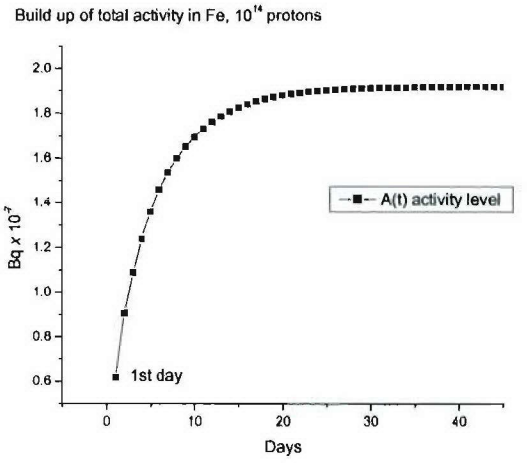


Fig. 20b Build up of total gamma ray activity in an iron MLC;$10^{14}$ 250 MeV protons delivered daily

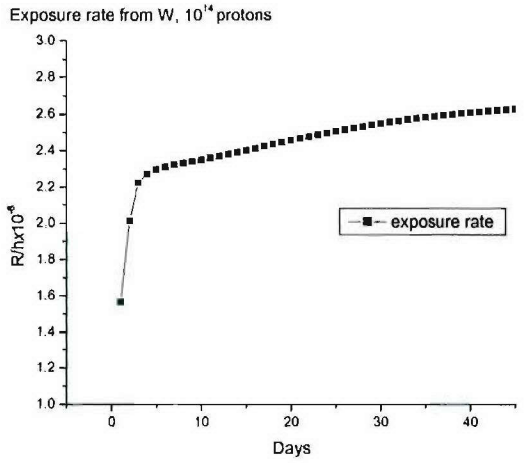


Fig. 21a. Exposure rate from a tungsten MLC; $10^{14}$ 250 MeV protons daily protons delivered daily

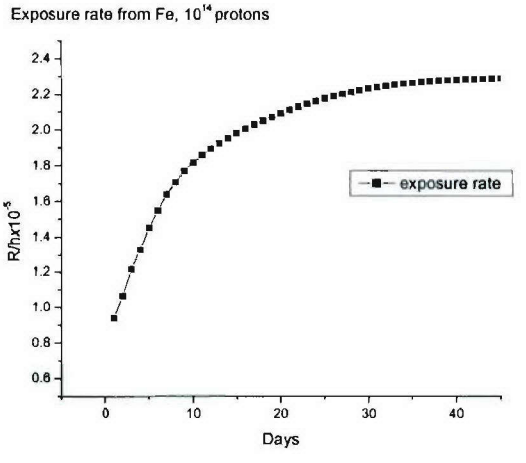


Fig.21b. Exposure rate from an iron MLC; $10^{14}$ 250 MeV protons delivered daily

Preliminary Monte-Carlo simulation of proton induced gamma ray emitting isotope production in iron, brass and tungsten were performed using the GEANT4 Monte-Carlo code. The same isotopes were produced in these Monte-Carlo simulation as derived from the published cross-section data.

E. Validation work at WRAMC

Monte Carlo simulation techniques are flexible tools offering an efficient method of testing clinical dose profiles, without the need of costly equipment and many man-hours of support needed for experimental measurement. Our work thus far has dealt primarily with determining a set of criteria that any simulation tool must meet for clinical proton radiotherapy research, implementing a set of benchmarks for testing the code, and finally forming a comparison of several available simulation tools to choose the most appropriate for our research. The following is a list of items completed to meet these goals.

(1) Criteria for choosing an appropriate simulation tool were determined according to physical parameters of the necessary clinical dose profile: (a) resolution of the distal edge profile, determined largely by energy loss straggling and multiple scattering; (b) primary contribution to the dose intensity via electronic energy loss processes, and; (c) contributions from secondary dose originating from relatively high energy nuclear interactions between the primary radiation and the dose delivery system and tissue.

(2) Three different proton Monte Carlo transport simulation codes were installed and benchmarked against experimental results: (a) SRIM/TRIM (J. Ziegler and Biersack)[22] which does not include nuclear interactions; (b) PTRAN, developed at the National Institute of Standards and Technology (M. Berger)[23], and includes a rudimentary model of nuclear interactions, and; (c) GEANT (CERN), an open source, highly modular simulation framework capable of handling complex geometries and multiple nuclear interaction models.

(3) Cross-comparison of simulation codes was performed to determine the range of validity and the best to use for simulation of dose for treatment planning. All accurately model the electronic energy loss of protons in water with respect to previous experimental results. Both PTRAN and GEANT model the nuclear interaction component quite well, however PTRAN lacks the flexibility to incorporate heterogeneous materials such as mixtures of tissue and bone.

(4) Results of predicted dose from those codes suggest GEANT is the preferred Monte Carlo dose modeling tool because of its innate flexibility and robustness noting it supports incorporation of the complex media to be studied.

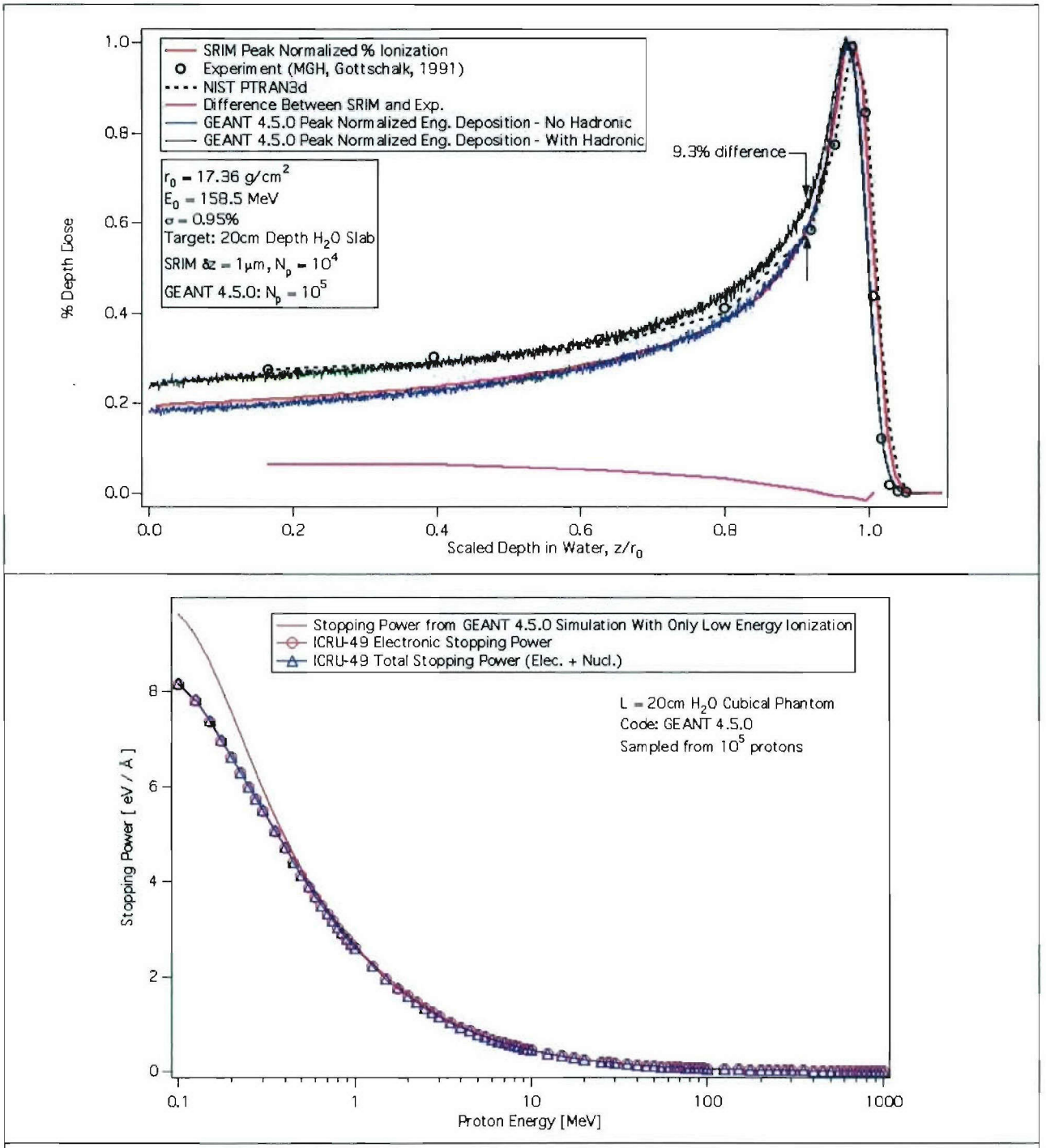


Fig. 22. Comparison of various simulation programs with data (top) and a comparison of stopping power from ICRU 49 (Ref. 9) with that used in GEANT4 (lower).

F. Web-based clinical trials

Only 2-4% of adult cancer patients enroll in clinical trials in the United States and many patients are never offered information on trials for which they may be eligible. Many patients are now accessing the Internet to educate themselves on cancer clinical trials and are exploring the availability of proton therapy. OncoLink (http://www.oncolink.org) is the web based educational resource from the University of Pennsylvania Cancer Center and serves between 1.5-2 million pages per month to over 385,000 unique IP addresses. OncoLink launched one of the first clinical trials matching resources on the Internet that allowed patients to enter demographic data through a secure Internet connection and match to clinical trials based on the inclusion and exclusion criteria of each trial.

Between 12/01 and 2/05, 4987 patients submitted online profiles to OncoLink and were matched for potential enrollment in clinical trials. The most common diagnoses of patients using this system included colorectal cancer (14%), breast cancer (13%), and lung cancer (10%). Of these patients, 548/4987 (11%) applied for trial enrollment after review of their matches to specific trials.

These data on conventional cancer treatments show that patients are willing to use the Internet for matching into clinical trials. We expect that the Internet will provide an important means to recruit patients to proton therapy clinical trials in the future. As regional clinical proton centers are constructed this resource could also serve as a central registry for proton therapy clinical trials.

**Key Research Accomplishments**

- Comparative analysis of proton transport simulation models has been completed. Current simulation work at WRAMC is concentrating on developing validated estimates of dose in heterogeneous media and related design criteria needed for phantom measurements.
- Installation and validation of GEANT4 at HUP using both RedHat and Suse Linux operating systems and the ROOT code for analysis. These programs were validated by comparing results to published data.
- Successful coding of Multileaf Collimator leaf designs in GEANT4 with the capability to read an input file for changing leaf positions.
- Monte Carlo code used to determine neutron production in various potential materials used to fabricate proton MLC.
- Neutron energy spectra produced in iron, brass and tungsten calculated as a function of proton energy and the dose in water due to the neutrons generated in the MLC by high energy protons is presently being evaluated.
- The radiation exposure associated with proton induced radioactive gamma emitters in a MLC has been evaluated in iron and tungsten. The calculated exposure rates 10 cm

from a proton MLC fabricated with these materials is low < 0.02 and 0.003 mrem/hr for iron and tungsten, respectively. Personnel exposure to individuals working with an iron MLC will be < 40 mrem/yr and 6 mrem/yr with a tungsten MLC, which are very low for radiation workers.

- Four abstracts accepted for 2005 AAPM annual meeting in Seattle and one at the PTCOG meeting in Tokyo. Additional papers will be presented at the PTCOG meeting in December 2005.

**Reportable Outcomes**

The following abstracts based on work performed on this project have been accepted at scientific meetings:

1. Metz JM, McDonough J, Hampshire MK; "Utilization Of An Internet Based Cancer Clinical Trials Matching System: Implications For Proton Therapy". PTCOG meeting June 2005, Tokyo, Japan.
2. Baldytchev M, Bloch P, Maughan R, McDonough J; "Activation induced by proton interactions in a multi-leaf collimator in proton therapy". AAPM meeting July 2005, Seattle WA.
3. Avery S, Goulart D, Maughan R, McDonough J; "Design characteristics of a MLC for proton therapy". AAPM meeting July 2005, Seattle WA.
4. McDonough J, Goulart D, Baldytchev M, Bloch P, Maughan R; "Monte-Carlo investigation of proton-generated radioactivity in a multileaf collimator". AAPM meeting July 2005, Seattle WA.
5. Goulart D, Avery S, Maughan R, McDonough J; "Validation of a Monte Carlo algorithm for simulation of dispersion due to scattering of a monoenergetic proton beam". AAPM meeting July 2005, Seattle WA.

**Conclusions**

This report documents the work that has been accomplished during the first year of the project to design an MLC for proton radiotherapy. Much of the first half of this initial year was spent organizing the necessary equipment and personnel to perform the tasks outlined in the Statement of Work. Once organized we validated the GEANT4 Monte Carlo simulation toolkit and demonstrated that it will prove to be a very powerful instrument to help us solve a variety of design questions. Some of those questions were addressed in this report including the production of secondary neutrons and radioactive isotopes from different potential materials making up the MLC leaf.

Finally, collaboration has begun between HUP and WRAMC that will lead to the full integration of the WRAMC staff in the treatment planning process that will occur when the proton facility comes online.

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**Databases used for reference:**

1. Experimental Nuclear Reaction Data (EXFOR/CSISRS) http://www-nds.iaea.org/
2. LANL T-2 database: http://t2.lanl.gov/data/data.html
3. Durham Database Group, at Durham University (UK). http://www-spires.dur.ac.uk/hepdata/reac2.html
4. Radiological data at http://www.martindalecenter.com/ and http://education.jlab.org/itselemental/index.html.
5. Periodic table at http://pearl1.lanl.gov/periodic/default.htm

**Appendices**

none